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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/602,508	06/23/2000	Susan Bonner-Weir	10276-029001	9106

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EXAMINER
AFREMOVA, VERA

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 10/22/2002 18

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/602,508	Bonner-Weir et al.
Examiner	**Art Unit**
Vera Afremova	1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 7, 2002* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-64* is/are pending in the application.

4a) Of the above, claim(s) *1-13, 27, and 28* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *14-26 and 29-64* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *16,17*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-64 are pending.

Claims 1-13, 27 and 28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected invention. Election was made without traverse in Paper No. 7 filed 8/03/2001.

Claims 14-26 as amended and new claims 29-64 [Paper No. 11 filed 4/11/2002] were subject to second restriction requirement [Paper No. 14 mailed 7/02/2002].

Election/Restriction

In response to the applicants' arguments [Paper No. 15 mailed 8/07/20002] that the second restriction requirement is not proper because the pancreatic cells and pancreatic cells free from islets cells are neither different nor distinct as starting cellular material in the method for producing islets cells, the claims of the Groups I and II [Paper No. 14 mailed 7/02/2002] have been rejoined.

Claims 14-26 and 29-64 are under examination in the instant office action.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 14, 16, 17, 21-26, 29, 31, 32, 36-40 are rejected under 35 U.S.C. 102(b) as being anticipated by Kerr-Conte et al. [IDS-AH].

Claims are directed to a method for obtaining pancreatic islets cells from dedifferentiated pancreatic cells wherein method comprises step of providing pancreatic cells, allowing the pancreatic cells to proliferate to form a population of dedifferentiated pancreatic cells, adding a component of extracellular matrix to the population of dedifferentiated pancreatic cells and culturing cells to obtain islet cells. Some claims are further drawn to the population of dedifferentiated pancreatic cells which express a marker indicative of expansion such as cytokeratin in the method for obtaining islets cells. Some claims are further drawn to the cultivated cells which forms buds or which are hormone positive or express insulin or glucagon. Some claims are further drawn to the use of extracellular components comprising laminin or a basement membrane derived substance/composition prepared from EHS (Engelbert-Holm-Swarm tumor cell.

Kerr-Conte et al. [IDS-AH] disclose an *in vitro* model method for neogenesis of pancreatic islets cells wherein method comprises step of providing population of pancreatic cells derived from human islets preparations, allowing the pancreatic cells to proliferate to form a population of dedifferentiated pancreatic cells as evidenced by staining with cytokeratin, adding a component of extracellular matrix to the population comprising dedifferentiated pancreatic cells by resuspending or overlaying the cells and further culturing the cells to obtain islet cells as evidenced by formation of fused budding structures with tubular network structures and hormone

positive cells including insulin and glucagon producing cells. The cited reference teaches expansion of ductal epithelial cells derived from mixed pancreatic preparation comprising ductal cysts and islets and further reorganization of the expanded dedifferentiated cellular material into islets cells.

Thus, the cited reference is considered to anticipate the claimed invention because it comprises identical steps as claimed such as expansion of the population of dedifferentiated pancreatic cells or ductal epithelial cells as evidenced by positive staining with cytokeratin and producing islets cells from dedifferentiated pancreatic cells or ductal epithelial cells in the presence of extracellular matrix as evidenced by morphological reorganization and hormone production.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 14, 16, 17, 21-26, 29, 31, 32, 36-42, 44, 45, 47-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kerr-Conte et al. [IDS-AH] and Gmyr et al. [IDS-AG].

Claims 14, 16, 17, 21-26, 29, 31, 32, 36-40 as explained above. Claims 41, 42, 44, 45, 47-51 are drawn to the use of pancreatic cells free from islets cells in the method for obtaining islets cells.

The cited reference by Kerr-Conte et al. [IDS-AH] is relied upon as explained above. In particular, it teaches the use of mixed population of pancreatic cells for neogenesis of islet cells. However, it clearly indicates that the neogenesis of islets cells or neogenesis of endocrine cytodifferentiation raises from the expanded ductal epithelial cells which are positive for cytokeratin or which are positive for marker of dedifferentiated pancreatic cells. Thus, the references clearly teaches or suggests the use of pancreatic cell populations free from islets cells for neogenesis of islet cells.

The reference by Gmyr et al. [IDS-AG] teaches an *in vitro* method for dedifferentiation of exocrine cells or pancreatic cells free islets cells as evidenced by expression of cytokeratin markers. It also suggests the use of the expanded populations of dedifferentiated exocrine cells which are free islets cells for further endocrine differentiation into hormone producing islets cells.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use pancreatic cells free from islets cells or pancreatic cells separated from islets cells for production of islets cells or for neogenesis of islets cells as suggested by the prior art {Gmyr et al. [IDS-AG]; Kerr-Conte et al. [IDS-AH]} with a reasonable expectation of success in producing differentiated islets cells capable to secrete hormones because the newly formed hormone producing islets cells raise from the expanded and reorganized pancreatic ductal epithelium cells as taught by the prior art {Gmyr et al. [IDS-AG]; Kerr-Conte et al. [IDS-AH]}. One of skill in the art would have been motivated to produce new

islets cells for the expected benefit of regenerating pancreatic function including treating clinical exocrine pathologies.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Claims 18-20, 33-35, 46, 52-56 and 61-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kerr-Conte et al. [IDS-AH] and Gmyr et al. [IDS-AG] as applied to claims 14, 16, 17, 21-26, 29, 31, 32, 36-42, 44, 45, 47-51 above, and further in view of US 4,829,000 [B] and US 5,681,587 [IDS-AB] and US 6,077,692 [C].

Claims 14, 16, 17, 21-26, 29, 31, 32, 36-42, 44, 45, 47-51 as explained above. Claims 18-20, 33-35, 46 and 61-64 are further drawn to the use of extracellular components comprising laminin, basement membrane derived substance or composition prepared from EHS (Engelbert-Holm-Swarm tumor cells), collagen, entactin, nitogen and heparin sulfate proteoglucan. Claims 52-56 are further drawn to the use of glucose and growth factors such as epidermal growth factor (EGF) or hepatocyte growth factor (HGF) or keratinocyte growth factors in the media for growth and expansion of pancreatic cells

Both cited references Kerr-Conte et al. [IDS-AH] and Gmyr et al. [IDS-AG] teach the use of basic DMEM or RPMI culture medium ingredients including glucose and the use of growth

factors including EGF and HGF in the media for growth and expansion of pancreatic cells. The cited references Kerr-Conte et al. [IDS-AH] and Gmyr et al. [IDS-AG] also teaches the use of extracellular matrix in the process of islets cells neogenesis such as collagen and matrigel {Kerr-Conte et al.} or 804G matrix {Gmyr et al.}.

However, the cited references Kerr-Conte et al. [IDS-AH] and Gmyr et al. [IDS-AG] are silent with regard to particular composition or components of the extracellular matrix preparations matrigel or 804G matrix. But the cited patents US 4,829,000 [B] and US 5,681,587 [IDS-AB] are relied upon to demonstrate that matrigel and 804G matrix comprise laminin, basement membrane derived substances prepared from EHS (Engelbert-Holm-Swarm tumor cell), collagen, entactin, nitogen, heparin sulfate proteoglucan, etc. For example: see US 4,829,000 at col. 3, lines 47-54; col.4, lines 4-7, lines 27-30. See US 5,681,587 at col. 2, lines 33-46; col.4, lines 15-18. The cited patents teaches the use of extracellular matrix material such as matrigel and/or 804G matrix for culturing and expanding various populations of animal cells including pancreatic cells and/or islets cells.

The cited references Kerr-Conte et al. [IDS-AH] and Gmyr et al. [IDS-AG] teaches the use of various growth factors in the method for producing islets cells. But they are silent with regard to keratinocyte growth factor. However, the cited patent US 6,077,692 [C] teaches that keratinocyte growth factor induces and promotes growth and expansion of pancreatic cells including ductal epithelial cells.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use the presently claimed basic medium ingredients, growth factors and extracellular matrix materials in the method for producing islets cells because these ingredients and materials have been known and successfully used the methods for producing pancreatic cells including islets cells as taught by all cited references. One of skill in the art would have been motivated to use the presently claimed ingredients and materials for the expected benefit of growing pancreatic cells and/or regenerating pancreatic functions. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary. The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Claims 58-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kerr-Conte et al. [IDS-AH] and Gmyr et al. [IDS-AG] as applied to claims 14, 16, 17, 21-26, 29, 31, 32, 36-42, 44, 45, 47-51 above, and further in view of WO 96/40872 [IDS-AD] and Carlsson et al. [W].

Claims 14, 16, 17, 21-26, 29, 31, 32, 36-42, 44, 45, 47-51 as explained above. Claims 58-60 are further drawn to the expression of particular markers of dedifferentiated pancreatic cells such as IPF-1, Pref-1 or lack of insulin.

The primary references Kerr-Conte et al. [IDS-AH] and Gmyr et al. [IDS-AG] teach the methods for producing islets cells from pancreatic cells including pancreatic cells free from islets

cells wherein expansion of the dedifferentiated pancreatic cells or of pancreatic ductal epithelial cells is evidenced by expression of cytokeratin {Kerr-Conte et al. [IDS-AH]; Gmyr et al. [IDS-AG]} or by lack of insulin before endocrine differentiation {Kerr-Conte et al. [IDS-AH]}. They are silent with regard to expression of markers IPF-1 and Pref-1 by dedifferentiated pancreatic cells including ductal epithelial cells.

However, WO 96/40872 [IDS-AD] teaches expression of IPF-1 marker by the expanded population of pancreatic progenitor cells as a critical event during pancreas development (page 27, lines 5-10).

Carlsson et al. [W] teaches expression of Pref-1 proteins by pancreatic progenitor cells during pancreatic developments and it teaches that the Pref-1 positive cells further develop into insulin producing differentiated cells.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use the presently claimed markers in the method for producing pancreatic islets cells because these markers have been know and demonstrated as critical in the development of pancreatic cells and in the development of biological functions of pancreatic cells including hormone production. One of skill in the art would have been motivated to use the presently claimed markers for selection of population of pancreatic cells which are restricted to differentiation towards hormone producing pancreatic islets cells for the expected benefit of producing pancreatic cells including islets cells and/or regenerating pancreatic functions including hormone production. Thus, the claimed invention as a whole was clearly

prima facie obvious, especially in the absence of evidence to the contrary. The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Claims 15, 30, 43 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kerr-Conte et al. [IDS-AH] and Gmyr et al. [IDS-AG] as applied to claims 14, 16, 17, 21-26, 29, 31, 32, 36-42, 44, 45, 47-51 above, and further in view of US 4,439,521 [IDS-AC] and Kerr-Conte et al. [IDS-AY].

Claims 14, 16, 17, 21-26, 29, 31, 32, 36-42, 44, 45, 47-51 as explained above. Claims 15, 30, 43 and 57 are further drawn to the grow of adherent pancreatic cells till 70% confluency.

The cited references by Kerr-Conte et al. [IDS-AH] and Gmyr et al. [IDS-AG] teach method for producing islets cells or for neogenesis of islets cells in the presence of extracellular matrix material. The reference by Gmyr et al. [IDS-AG] teaches that expansion allows to obtain sufficient number of cells for further differentiation. However, the cited references are not particularly clear with regard to confluency of growth of the expanded cells populations and with regard to selection based on adherence to container.

However, the cited patent US 4,439,521 [IDS-AC] teaches that production or regeneration of islets cells occur after adherence and expansion of pancreatic cells till considerable confluency of about 50% or 60-70%, for example: see col. 9, lines 15-23. The patent also teaches a selection of adherent pancreatic cells for further producing islets cells by

teaching step of discarding cells which remain unattached during expansion of ductal cells (col. 5, lines 25-30).

The reference by Kerr-Conte et al. [IDS-AY] teaches expansion of ductal epithelial cells in monolayer culture or as adherent cultures on plastic of a culture container before the incorporation of extracellular matrix and additional growth factors permitting differentiation of pancreatic cells in the *in vitro* model for islet cell neogenesis.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to expand the pancreatic cells in adherent monolayer culture before differentiation in the method for producing pancreatic islets as taught and suggested by the cited prior art because expansion in adherent monolayer cultures allows for a considerable increase of pancreatic cells intended and/or restricted to further differentiation towards hormone producing pancreatic islets cells. One of skill in the art would have been motivated to expand the population of pancreatic cells for maximizing numbers of differentiated hormone producing cells for the expected benefit of producing pancreatic cells including islets cells and/or regenerating pancreatic functions including hormone production. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351. The examiner can normally be reached on Monday to Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vera Afremova,

Art Unit 1651

October 16, 2002

IRENE MARX
PRIMARY EXAMINER